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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	
NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/511,719	KIM ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-41 and 44* is/are pending in the application.

4a) Of the above claim(s) *39-41 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-38* is/are rejected.

7)☒ Claim(s) *34-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/18/04* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/24/08 has been entered.

Status of the Claims

2. Claims 33, 36, 40, and 44 were amended in the instant Reply. Claims 42-43 were canceled. Accordingly, claims 33-41 and 44 are pending in the application, with claims 39-41 and 44 currently withdrawn (see below). Claims 33-38 are subject to examination below.

Claims 37-38 are being examined to the extent that they read on the elected species of SEQ ID NO:3.

Election/Restrictions

3. As amended in the instant Reply, claim 40 now recites a kit that comprises "a recombinant protein of βig-h3 fas-l domain consisting of 1 to 10 linked 4th fas-l domains encoded by SEQ ID NO:6". Applicant has elected for consideration βig-h3 *per* se, SEQ ID NO:3, as the species of recombinant protein (see Applicant's Reply dated 8/11/06 at page 4 and the restriction requirement mailed 7/14/06). As a result of the instant amendments, claims 40-41

no longer read on the elected species since claim 40 no longer recites that the recombinant protein may be βig-h3 *per* se.

Accordingly, claims 40-41 withdrawn from consideration as being directed to a non-elected species. See 37 CFR 1.142(b) and MPEP § 821.03.

Objections/ Rejections Withdrawn

4. The rejections of claims 42-43 are moot in light of Applicant's cancellation of the claims.

5. The objections to claims 33 and 40 have been obviated by Applicant's amendments.

6. The rejection of claim 36 under § 112, 1st paragraph as containing new matter has been obviated by Applicant's amendments.

7. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

8. The rejections of claims 40-41 under § 103(a) are moot in light of the withdrawal of the claims as being drawn to a non-elected species.

Priority

9. The present application was filed on 11/26/2004 and is a national stage (371) application of PCT/KR02/01975, filed 10/22/02. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Korean Application No. 2002/21488, filed on 4/19/2002.

Information Disclosure Statement

10. Applicant's Information Disclosure Statement filed 6/24/08 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

Citation BB (Gilbert et al.) has been lined through to avoid duplication citation, as the reference is already of record (see PTO-892 dated 10/18/06).

Drawings

11. The drawings are objected to because in Figure 17, the different plot lines in the legend appearing in the upper left hand corner cannot be distinguished from each other, such it is difficult to determine what the plot lines in the Figure correspond to. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and

informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

12. Claims 34-38 are objected to because of the following informalities: the dependent claims employ the terminology "The method as set forth in" to refer to preceding claims, which is ambiguous. The language "The method of claim X" is suggested.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention relates to the observation of elevated βig-h3 levels in the context of disease. In particular, in Example 4-1, the specification discloses the results of an experiment in which βig-h3 levels were measured in subjects with type II diabetes. Some of the diabetic patients already had symptoms of renal disease (i.e., after "clinical troubles" as indicated by the presence of microalbuminuria, overt proteinuria, or outright chronic renal failure), while

other diabetic patients had no symptoms of renal disease. Applicant reports that all diabetic populations had elevated urinary βig-h3 levels as compared to normal controls (Table I).

In Example 4-2, diabetes was induced in an animal model by injecting the diabetes-inducing drug streptozotosin. Increased levels of urinary βig-h3 were seen in the diabetic-induced rats (Figures 13-14).

The claims as currently amended are drawn to methods and kits for diagnosing damage to the kidneys at an early stage prior to showing "clinical troubles", based on measurement of βig-h3 in urine samples, and wherein elevated levels of βig-h3 are diagnostic of kidney disease.

One skilled in the art at the time of the invention would also appreciate that in order to be employed in diagnosis, a biomarker must be not only altered in the disease state (i.e., sensitive to the presence of disease), but must also be specific to the disease to be diagnosed. See for example Mayeux et al. ("Biomarkers: Potential uses and Limitations"; NeuroRx (2004); Vol. 1, pages 182-188), which teaches that biomarkers are validated by a number of criteria, including the extent to which the biomarker correlates with the specific disease under study (page 186, left column, the first two full paragraphs):

> The evaluation of the validity of a biomarker is complex…false positives and false negatives as well as positive and negative predictive power should also be estimated…sensitivity and specificity tell us the accuracy of the test but not the probability of disease. For that we need to estimate the predictive values (positive and negative). Positive predictive value (PPV) is the percentage of people with a positive test who actually have the disease. This provides us with information about the likelihood of the disease being present if the test is positive. Negative predictive value (NPV) is the percentage of people with a negative test who do not have the disease. Increasing the prior probability will increase the PPV but decrease the NPV, assuming that the sensitivity and specificity remain unchanged. Similar changes in the predictive values occur with changes in the prevalence of a condition as will be discussed in screening.

Thus, those of skill in the art recognized that in order to be useful as a diagnostic biomarker, a candidate must predict accurately the number of people who do (or do not) have a particular disease. To determine this, it would clearly be necessary to compare levels of the candidate in the disease state and in healthy controls, so that not only the sensitivity and specificity but also the positive and negative predictive value of the marker can be assessed as discussed by Mayeux et al.

The prior art also recognized that the demands placed on biomarkers to be used for the purpose of *diagnosis* are much higher than for those biomarkers used to monitor known disease in existing patients. See LaBaer et al. (Journal of Proteome Research 2005, 4, 1053-1059, of record), especially at page 1054, "Disease Diagnosis".

In the instant case, the data presented in the specification do not reasonably enable the use of βig-h3 as a biomarker of kidney disease because appropriate controls are lacking that would support a nexus to this disease.

In particular, Applicant claims methods of detecting kidney disease in patients prior to showing "clinical troubles", which would read on patients who have no symptoms of kidney disease such as microalbuminuria or proteinuria (see in particular the specification at the paragraph bridging pages 38-39).

In Table I, such patients are represented in the **"Type II DM"** population in the third line. The data show that βig-h3 levels were elevated in these patients who had no symptoms of kidney disease. Applicants conclude from these data that βig-h3 is an *early* marker of renal disease since it is detectable even in the absence of any clinical symptoms of renal disease (such as microalbuminuria or proteinuria). See discussion on page 38, line 14 to page 39, line 5.

The Examiner finds that the data presented do not reasonably support such a conclusion, for the following reasons.

It must be reiterated that the "Type II DM" patients without any symptoms of renal disease were known to have diabetes; however, their kidney disease status was *unknown*. Only the βig-h3 levels for the entire population are reported.

Not all of the patients in the "Type II DM" population studied would also have been suffering from early kidney disease, since the American Diabetes Association reports that only about 20-30% of patients with diabetes also develop evidence of nephropathy (kidney disease) ("Nephropathy in Diabetes"; Diabetes Care Vol. 27, Supplement 1 (2004), pages S79-S83, of record; especially at page S79, left column). Therefore, only some of the patients in the population actually had the disease under study (early kidney disease), but data are reported only for the population as a whole. The specification notably lacks retrospective data in which the diabetic subjects without any overt clinical symptoms were monitored over time for subsequent development of kidney disease, and in which βig-h3 levels were assessed in terms of those subjects who went on to develop kidney disease and those who did not.

Similarly, in the experiment of Example 4-2, βig-h3 levels were measured in rats with induced diabetes, but there is no independent verification of the presence of kidney disease. As such, the data showing elevated levels in diabetes-induced rats could equally suggest a potential correlation between βig-h3 and *diabetes*, rather than between βig-h3 and *early kidney disease*. Yet because no retrospective studies were performed, and no examination of subjects with early kidney disease but *without diabetes*, it has not been reasonably confirmed whether elevation of βig-h3 occurs in response to diabetes, in early kidney disease, or in both disease conditions.

It is unclear how a candidate biomarker could be validated for diagnosis of disease by studying patients whose disease status is unknown; how can altered levels be correlated with the presence of disease if it is not known which patients have the disease and which do not? Without examining disease vs. control subjects (in this case, patients with early renal disease vs. patients without renal disease), it is not possible to determine whether only diabetics with early renal disease have elevated βig-h3 levels, or alternatively whether all diabetic subjects have elevated levels (in which case elevated βig-h3 would not be useful as an early stage kidney damage marker since it would not be specific to the disease).

The breadth of the claims is also at issue because the claims encompass diagnosis of kidney disease in any patient population, yet the specification only examined subjects with diabetes. The teachings of the specification regarding *diabetic kidney disease* are not commensurate with the scope of the claims drawn to any type of kidney disease; there is no indication that βig-h3 might also be elevated in asymptomatic kidney disease patients without co-morbid diabetes.

The specification also lacks direction and guidance with regard to how βig-h3 can be used as a marker of early kidney disease since it fails to discriminate diabetes from early kidney disease. LaBaer et al. (discussed above) also teach that for biomarkers to be used for diagnosis, quantitative values must be established that set the boundary between a positive and negative test (see page 1054, "Disease Diagnosis"). In the instant case, because the specification does not show whether βig-h3 values differ in diabetics with early kidney disease vs. diabetics without kidney disease, guidance is lacking with regard to what values of βig-h3 might indicate early kidney disease and what values would be considered normal.

Furthermore, the specification posits that βig-h3 can be used as a diagnostic marker not only of renal disease, but also of hepatic diseases, rheumatoid arthritis, and cardiovascular diseases. Because of this, and in addition to the issues discussed above regarding insufficiency of disclosure that βig-h3 is a sensitive marker of kidney disease (i.e., that it is elevated in the disease state), there is insufficient evidence here that βig-h3 is a specific marker of kidney disease. Given that βig-h3 is apparently elevated in a number of disparate disease conditions, and when taken together with the lack of guidance with regard to *differential diagnosis*, one of ordinary skill in the art would face an undue burden of experimentation in determining whether a subject with elevated levels of βig-h3 should be diagnosed early kidney disease, or alternatively hepatic disease, arthritis, or cardiovascular disease.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In the instant case, little is apparently known about the use of urinary βig-h3 for early stage diagnosis of kidney damage. However, the data fail to include appropriate controls that

would rule out false positive findings. Levels of βig-h3 were examined only in subjects who were also known to have diabetes, and elevations were seen for all diabetic subjects with and without signs of kidney disease. It not apparent that βig-h3 is specifically elevated in early kidney damage, as opposed to being generally elevated in diabetes.

The prior art also recognized that experiments to validate and test a candidate biomarker for clinical application are not of a routine nature. For example, Bast et al. (Clin Cancer Res 2005; 11(17), 6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p. 6105, right column). See also LaBaer et al. (discussed above), which teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor, and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p. 1053, see the paragraph bridging the left and right columns). Baker (Nature Biotechnology 2005; 23(3), 297-304) also speaks to the unpredictability involved in clinically applying biomarkers (see p. 298, the section "Walking on Thin Ice"):

> Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is," says Ole Vesterqvist..."You start walking, and you get comfortable. Then you break through.

Thus, the state of the art teaches the unpredictability associated with the clinical use of biomarkers even after a biomarker has been correlated with a specific disease state. These references speak not only to the unpredictability associated with validating candidate biomarkers for clinical use, but also to the large quantity of experimentation involved in doing so.

Regarding the presence or absence of working examples, the specification does not disclose any examples in which subjects whose renal disease status was unknown were diagnosed based on βig-h3, either prior to or after symptoms of disease were observed.

In summary, the experiments lack adequate controls; the "Type II DM" patients represented in Table I were known to have diabetes, but their kidney disease status was unknown. Applicant investigates whether βig-h3 levels are associated with early kidney disease, but does not verify the presence of kidney disease (by reference to another known marker, for example). In addition, the specification posits that βig-h3 is a marker of large number of different diseases, which raises additional issues in regards to differential diagnosis. For these reasons, one or ordinary skill in the art would face an undue burden of experimentation in using βig-h3 to diagnose kidney damage at an early stage of disease because Applicant has not reasonably confirmed that βig-h3 is a sensitive or specific marker of early kidney disease.

15. Claims 33-38 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the preceding for detailed analysis of the teachings of the specification. In regards to written description, the specification fails to show actual reduction to practice of the claimed invention because there is no teaching in which diabetic patients had early stage kidney damage prior, and therefore no correlation shown between βig-h3 and the

disease to be diagnosed. The data do not reasonably confirm a nexus between βig-h3 and early stage kidney disease. Although βig-h3 levels were analyzed in diabetic patients who had no symptoms of kidney disease, this does not represent an actual reduction to practice because the presence of kidney disease in these subjects was not verified. Furthermore, there is no actual reduction to practice of methods of *diagnosis*—i.e., determining the presence of disease in subjects in unknown subjects.

There is also evidence of unpredictability in the art, as discussed in detail above. Despite such unpredictability, the specification posits that βig-h3 can be used as a diagnostic marker not only of renal disease, but also of hepatic diseases, rheumatoid arthritis, and cardiovascular diseases. If βig-h3 is a non-specific marker that is common to all of these disparate diseases, it is unclear how it could be used to predictably diagnose any of them.

For all of these reasons, one skilled in the art would not envisage possession of methods of using βig-h3 to diagnose early stage kidney disease because the specification fails to show that this protein is elevated in this disease in either a specific or sensitive manner.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim 33 recites a method for detecting damage to kidneys "at an early stage prior to showing clinical troubles". The term "early" is a relative term which renders the claim indefinite.

The term "early" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although the term "early" is described in the claim to be "prior to showing clinical troubles", this terminology is vague and indefinite; the specification does not provide a specific or limiting definition of "clinical troubles". It is not clear what would be considered "clinical troubles"—for example, would the presence of any symptom represent "clinical trouble", or alternatively, only symptoms severe enough to require medical attention? Because it is not apparent what would be considered "clinical troubles", reference to the disease being "prior to clinical troubles" does not provide a standard for understanding the scope of the term "early".

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/791043 in view of Ramsden et al. (US 4,640,909).

The '043 application claims a method for diagnosing disease, including kidney disease (i.e., damage to the kidneys) by measuring the level of βig-h3 in a sample as compared to that of a control sample (see especially claims 8-12).

The '043 application differs from the instant claims in that it fails to specify what type of sample is assayed for βig-h3, and therefore fails to specifically teach a urine sample. In addition, the '043 application refers to comparing βig-h3 levels with those in control samples, but does not specify whether an increase or decrease is indicative of disease.

Ramsden et al. teaches that urine samples are noninvasive and convenient. See column 1, lines 15-16.

Therefore, it would have been obvious to one of ordinary skill in the art to employ a test sample that is a urine sample in the method of the '043 application for convenience and because urine samples can be collected in a noninvasive manner.

Furthermore, upon comparing βig-h3 levels with those in control samples as taught in the '043 application, it would require no more than routine experimentation to determine whether levels were increased or decreased in correlation with disease. Consequently, when taken together with the general knowledge in the art, it would also have been obvious to one of ordinary skill in the art to diagnose kidney disease when βig-h3 levels were elevated as compared to control samples.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

21. Applicant's arguments filed 6/24/08 have been fully considered.

22. With respect to the rejections of claims 33-38 under § 112, 1st paragraph (enablement), Applicant's arguments have been considered but are not persuasive.

Applicant argues that in addition to the data presented in Table I, Example 4-2 of the specification must also be considered (Reply, pages 8-9).

This is not found persuasive because as would be appreciated by the person of ordinary skill in the art, assessment of whether a candidate is a marker of disease requires a comparison of protein levels in the presence and in the absence of the disease. As in the experiment reported in Table I, the experiment of Example 4-2 studied βig-h3 levels in subjects with *diabetes* but does not break down or report which of the subjects actually had *early kidney disease* and which did not. Consequently, the data do not represent a comparison of disease vs. normal controls. It cannot be concluded from such data whether βig-h3 levels are elevated in response to *early kidney disease* since the presence of kidney disease was not independently verified; one could just as easily surmise that the elevation of βig-h3 was a consequence of *diabetes*.

Applicant refers to MPEP 2164.02, arguing that when a particular model is correlated with a specific condition, it must be accepted as such absent evidence to the contrary (Reply, page 9). Such arguments are not on point because the Office does not contend that there is insufficiency of disclosure on the basis of *in vitro* vs. *in vivo* data or because of the use of animal

models. However, in regards to the animal model data of Example 4-2, Applicant has not correlated the model with the specific condition under study since βig-h3 levels are reported only for the aggregate population of diabetes-induced rats, no correlation is shown for early renal disease.

Applicant also points to Example 4, pages 38-45, as providing guidance with regard to the selection of cut-off values for diagnosing early renal disease (Reply, pages 9-10).

This is not found persuasive because Examples 4-1 and 4-2, as discussed in detail above, do not provide guidance with regard to appropriate cut-off values since they do not discriminate between diabetics with early renal disease vs. diabetics without early renal disease. Furthermore, Examples 4-3 and 4-5 (pages 40-45) involved subjects who already had known kidney disease, i.e., were not "prior to showing clinical troubles"; relevance is not seen to the invention currently claimed.

23. With respect to the rejections of claims 33-38 under § 112, 2nd paragraph in regards to "early stage" renal disease, Applicant's arguments have been considered but are not persuasive. Applicant argues that this term is well known in the art and is clear when read in light of the specification (Reply, pages 11-12), to which the Examiner disagrees for reasons of record. Applicant also points to the instant amendments to modify this term by reference to "prior to showing clinical troubles", which is not persuasive since this language is also found to be vague and indefinite for reasons discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 6:00-2:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Mark L. Shibuya, Ph.D./
Supervisory Patent Examiner, Art Unit 1641